RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte SAUL TZIPORI,
RAMASWAMY BALAKRISHNAN, and
ARTHUR DONOHUE-ROLFE

Appeal 2006-2945
Application 10/041,958
Technology Center 1600

Oral Hearing Held: August 8, 2007

Before DONALD E. ADAMS, LORA M. GREEN, and NANCY J. LINCK, Administrative Patent Judges

ON BEHALF OF THE APPELLANT:

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The above-entitled matter came on for hearing on Wednesday, August 8, 2007, commencing at 9:05 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Carol A. Lowe, RPR.

JUDGE ADAMS: We're familiar with your issues. You have 20 minutes. And you can begin when you're ready.

MS. PABST: Okay. Again, we want to thank you all for the opportunity to be here today.

This is a case involving a product that we think is really, really important. And Dr. Tzipori is going to update you as far as where the clinical trials in the development of this product is as well as hopefully give a brief overview of the technology and some of the differences with the prior art and walk a little bit through the example data to show you where those important features are proven in the application and then hopefully answer any questions that you might have.

Again, the technology here was the discovery that a very bad disease, this HUS that resurfaced again last year with the spinach outbreaks, is caused not just by an organism E. coli that was known to cause this disease but the fact that the toxin -- that one of the several toxins in this organism, the Shiga-like toxin II, is critically important not to the disease of the diarrhea and infection but to the very, very bad side effects, the systemic complications that lead to death and permanent disability and that within that Shiga-like toxin II toxin that's so important to death and the systemic complications that the subunits that make up that toxin, the alpha and then there are several beta, are different in terms of their properties in terms of causing disease.

So that we not only have the discovery that the Shiga-like toxin

II in human infection which is different than other animals is critically important to the systemic side effects; but that the subunit A is critically important to prevention of these life-threatening side effects and that it can be blocked with the antibody to prevent these effects after infection has occurred, after the patient is sick and that the beta subunit primarily relates to the diarrhea, not the life-threatening part and, therefore, that one can administer human antibody, not just to the Shiga-like toxin II specifically, and keep people from developing the life-threatening complications; but that if you select the alpha subunit, you can prevent the life-threatening complications, not the diarrhea, not the disease in general, and that this is absolutely specific to humans and that the dosage is critical and that that dosage could be generally determined using this very specific baby pig model where the animal does not receive Colostrum at birth.

So with that being said, I'm going to turn it over to Dr. Tzipori.

DR. TZIPORI: Thank you. I made some notes, because it's not what I normally do for a living and just to make sure I keep it simple in terms of the terminology as well as really the message I want to get across here.

So I hope it won't take me too long. I have made some copies. If you would like to have, I'll be happy to hand them to you.

The link between this bacteria 0157 and kidney failure was identified in 1983. And it was shown that the infection causes bloody diarrhea in people. But in a percentage of -- of infected individuals, such as children in particular and the elderly, the infection can go on and, of course, kidney failure.

And about three to six percent of those that contract and develop kidney failure develop what we call HUS or hemolytic uremic

syndrome or kidney failure or death.

As a veterinarian I noticed the similarity back in 1985 between this infection and an infection which occurs naturally in piglets. And in collaboration with the CDC we started this work to see whether we could use the pig to identify some of the characteristics that are responsible for inducing the disease in one hand and the -- and the kidney damage on the other.

And so using the pig model we were able to establish as one of the two toxins that the bacteria produces which is the Stx2 -- is more critical for the development of the kidney failure and that antibodies against the toxin II will prevent that.

So we went ahead and used -- we got funded from NIH to develop human antibodies in transgenic mice. Transgenic mice are special mice that have been manipulated genetically to produce human antibodies instead of mouse antibodies. And, hence, they are much more acceptable for clinical use.

And -- and as a consequence of this work in 1996 we filed a patent with regard to the use of this approach to treat children that are presenting with bloody diarrhea; treat them with these antibodies and prevent the consequence -- the consequential development of -- of HUS which is the kidney failure.

Because of the period between the onset of diarrhea and the onset of the kidney damage is about four days we felt that if these antibodies are given at the onset of diarrhea or thereafter, we could protect those children from developing kidney failure.

And this was -- that proved to be really the case, because the piglet develops diarrhea first and then two days later develops neurological

symptoms which kind of -- really they are the same type of generic disease. I don't really want to go into the physiology of it.

So we were able to, in fact, with the antibodies, the human antibodies that we produced -- to treat piglets well after the onset of the diarrhea, 48 hours, in fact, after infection, and still protect them against the fatal complication that are associated with the toxin.

Now, the antibodies are produced against the toxin. And they are given systemically -- that means by injection -- to utilize the toxin that have got -- that was absorbed or got absorbed from the GI tract, from the gastrointestinal tract. I just want to illustrate to you.

So we got as far as really -- with funding from the National Institutes of Health to show that these antibodies are protective, but NIH does not fund product development beyond this point as they expect the private sector to license such potential therapeutic products.

The lack of IP for this product has so far precluded such an option. This situation has changed dramatically with the emergence of threats of bioterrorism after September 11.

The CDC and NIH have classified HUS, this disease that I'm talking about, as a potential threat and funded our group to continue to develop this therapeutic approach under the umbrella of countermeasure development against biothreat.

The additional fund allowed us to really, A, generate under GMP enough material to test in -- in human volunteers and also to conduct the phase one clinical trials in human adult volunteer which is expected to begin in two or three days -- two or three months.

We have institutional protocols developed by Tufts University and the National Institutes of Health for adults -- for these studies in adults.

And it's currently pending FDA approval.

To illustrate the significance of the disease and the urgent need for therapy I refer your attention to three outbreaks due to this infection which occurred late last year. One in particular which became known as the spinach outbreak originated in California's Green Growers' farm.

During August, September 2006 the outbreak of E. coli involving 26 states occurred which affected 200 people. Half of them, 51 percent, were hospitalized. 31, 16 percent, developed kidney failure. 22 of them were children and under five years of age. 30 percent of children developed kidney failure, eight in adults and so on. Four of them died, two of -- two of whom are children.

During this outbreak I got numerous calls from clinicians and physicians inquiring about the status of our antibodies be it through -- of course, through the literature.

And a consultant from the California legislature contacted me requesting information on progress and had asked whether the California legislature can be -- in any way help -- can in any way help accelerate the process, to speed up the approval process and the production of this treatment.

The truth of the matter is given the perceived limited market for such a drug -- it's really classified as often a drug -- no commercial entity is willing to license this product without the secured IP.

I could go on and touch on how we address the issue of -- regarding prior arts, but maybe I should leave that -- if you have any questions.

I also have a summary of what we were able to reveal through our work with regard to this infection and how the treatment fits in, but I

could leave that. I don't want to kind of continue with this monologue.

JUDGE ADAMS: Thank you.

MS. PABST: Okay. Then let me make a few remarks. And I think we probably laid out most of our position with respect to why we think this is patentable over the prior art.

The fact is obviously the claims are drawn to different subject matter. The limitations in the claims that we think are important in distinguishing the prior art -- the differences in the claims that distinguish over the prior art include obviously the fact that this is to humans.

As is mentioned in the briefs and again must be emphasized, the strings of E. coli in -- are -- E. coli -- everybody knows this -- it was discovered in sewers of Austin, Texas. That shows how long I've been around. And it affects everybody. It's in our gut naturally.

But there are differences in strains as to which strains cause virulent disease. And the fact is that the strains that cause this severe disease in humans are ones which attach to specific receptors in the gut.

So when one talks about these antibodies it's important to understand that it is a small, specific group of these E. coli that actually cause the disease.

So the antibody specificity must be to the antigen, to the SL -- the Shiga-like toxin II antigen in the strains which cause disease in humans. That is not made clear in any of the prior art. What is also not made clear --

JUDGE ADAMS: Krivan -- Krivan talks about the treatment of humans, but --

MS. PABST: He has a claim in which he says humans; but Krivan -- Krivan is very different, because Krivan is a general disclosure.

And we acknowledge, as we did in our art, that there is general

disclosure that says there are multiple toxins in these E. coli; that you want to make antibody to the toxin to try to block the disease.

This goes far beyond what's in the prior art. This is based on studies which are described in great detail in the application that show that it is the Shiga-like toxin II that causes the life-threatening illness.

It is the Shiga-like toxin II which is important for prevention of development of the life-threatening symptoms after infection has occurred.

There is no recognition in any of the prior art of the two critical features related to the Shiga-like toxin II, life-threatening complications and prevention after infection.

Krivan is associated with prevention of disease. He is working primarily with -- and there's nothing wrong with Krivan. Krivan is a good reference for what it teaches which is that if you give animals that are deprived of Colostrum antibody before the junctions close up that you can help prevent diseases that are caused by these E. coli.

And, again, it's perfectly valid for what it is; but it isn't a teaching, because there's no data that shows the criticality of human antigen, human Shiga-like toxin II.

And, of course, one of the things that's -- you know, looking through the record you see, the -- the toxins depending on the origin are used with different names.

So like in the birds art that was cited here, the Shiga-like toxin II there is really the Shiga-like toxin I in human -- in strains that affect humans.

So it's very important, again, to focus on human and the Shiga-like toxin II in strains that cause severe disease in humans and then focus on the fact that it is the subunit A. And, of course, we know we have claims to

B. And we have claims specific to A.

In these strains in causing severe disease in humans B is responsible for the diarrhea. A is responsible for the life-threatening complications.

And, as Dr. Tzipori made clear, this product is important. It will save lives. This is one of those few times when I, as an attorney, am privileged to work on something that will make a difference.

This one is important, because there was this significantly over the prior art which was based on the studies that are described in this application. There were subsequent studies we submitted in further proof of this.

The fact is that this subunit, the alpha subunit, and of the Shiga-like toxin II in strains causing disease in human is what will kill these people. It did kill people in 2006 and in 2005. It is a small population. There's no question about it.

JUDGE ADAMS: If I could interrupt you.

MS. PABST: Sure.

JUDGE ADAMS: You have five minutes remaining.

MS. PABST: That's fine. Those are the important features. I want to briefly touch on dosage. Dosage is a patentable limiting feature of these claims.

We have a number of precedential cases that focus on the fact that when you define something as an effective amount -- a dosage that is an effective amount that that distinguishes it over prior art not disclosing that effective dosage range.

For example, we have the -- and I don't know how to pronounce this word -- Aktiebolag v. Andrx Pharmaceuticals, a fed. circuit decision in

2003.

We have in re: Halleck which was the C.C.P.A. decision in 1970. We have Biagro Western Sales. That's a -- just a district court decision.

We have in re: Caldwell, C.C.P.A, 1963, Geneva Pharms -- Pharms, Inc., v. Glaxo Smith Kline, fed. circuit, 2003, and Minnesota Mining and Manufacturing Company, the fed. circuit decision in 2002.

Every one of these decisions was reported -- is a decision in which the language that it was an effective dosage imparted novelty and nonobviousness to those claims over the prior art. It is not a meaningless limitation.

It was not routine to discover -- the examiner has focused on the fact that it would be routine to optimize the dosage, but you have to have a starting point. You have to have a point at which you have efficacy in treatment.

And that starting point is described in these examples. It cannot be determined in vitro. It cannot be determined with mice. It had to be determined from these pig studies.

And that is what the inventors did in this case. They defined those starting dosage ranges. It turns out those dosage ranges are correct. Those are the ones that are going to be in the clinical trials. They are meaningful. And they are nowhere in the prior art. So we think that's an important limitation. Do you have any questions?

JUDGE ADAMS: So your position would be the dosages that -- I call it the Krivan --

MS. PABST: I'm sorry. I can't hear you.

JUDGE ADAMS: The K reference. Your position would be --

MS. PABST: I'm sorry. I still couldn't hear you.

JUDGE ADAMS: Your position would be that the dosages set forth in the primary reference, the K reference, the Krivan reference, are not -- are not equivalent to this effective amount in your claim --

MS. PABST: The prior art dosages cover a large dosage range which would, in fact, be toxic as well as ineffective.

And I think it's -- I don't have -- you all know the prior -- you know the case law quite well; that when you have a very large range, which -- much of which is not enabled for our indication, that that does not teach the selection of an effective dose range as defined by the claim.

And that's what these court decisions say as well; that where that limitation is important, as it is in this case, and where you cannot get there from the prior art that it is both novel and nonobvious.

And I think one other quick point which Dr. Tzipori touched on is when you look at nonobviousness -- and, of course, we're all looking at KSR v. Teleflex -- the fact is that this has been a disease that's been around for decades, a life-threatening disease with mortalities every year.

There is no effective treatment. This is the only treatment that the FDA is considering for treatment of this disease. There is longstanding but unmet need. This product is the only one that both recognition in the literature and in the scientific community --

JUDGE ADAMS: I missed that -- I missed that argument in your brief. It's not in there, is it?

MS. PABST: It actually is in the brief; page 9, last paragraph. Technology is very important. A need which has been known for many years but which there is no accepted product available to clinicians. It's being -- currently being developed using nonprofit research funds due to the

critical need for such a product.

That is the NIH funding that is being used for this. There was a licensee. And when we went on appeal they terminated the relationship. Because of that longstanding and unmet need the NIH stepped up on this and is funding the clinical development.

JUDGE ADAMS: Any questions? Okay. Thank you very much.

MS. PABST: Thank you.

(Whereupon, the proceedings at 9:25 a.m. were concluded.)